Dock (Geo.)

A CASE OF FATAL EPISTAXIS (FROM ENDOTHELIOMA OF THE NOSE), WITH A STUDY OF THE BLOOD.

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Read at the Meeting of the
Association of American Physicians,
Washington, D. C., May 3, 1899.

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G., aged thirty-seven years, hotel-keeper, was admitted to the University Hospital, January 10, 1899, on account of a severe nose-bleed.

His father died at eighty-nine years—cause unknown—his mother at fifty-two. She had a "rose cancer" over the pubes, which was removed. One brother is living at forty-five years, and one sister at forty-seven; both well. There has been no history of excessive bleeding in the family. Has one boy, thirteen years old; well.

G. was well as a child. Has had whooping-cough, measles, and mumps, with no sequelæ. No history of venereal disease. Smokes, and drinks whiskey in moderation.

Last August had hay fever (had had attacks for past three years), which became better after the first frost. Since then has had "catarrh." Five weeks ago his nose began to bleed; it bled for four hours, "filling a wash-basin." A week afterward there was another attack, which lasted three hours; two days later another, lasting two hours; another, three days later, lasted three hours; next day there was one lasting four hours. He then remained free from hemorrhage for ten days, when he had a severe attack, bleeding three hours. On January 8th bleeding began in the right nostril. This nostril now bleeds whenever the plug is removed, but, with two exceptions, the bleeding was always stopped by plugging. At present, January 11th, there is oozing of blood into the posterior nares, running down into the mouth.

January 12. Patient is very pale and weak; is very nervous; mind clear; both nostrils are plugged; there is marked *fetor ex ore*.

Height, 5 feet 9 inches; weight, one month ago, 218 pounds. Frame very large, musculature moderately developed, soft; panniculus very thick, especially over abdomen. Skin very pale, with slight yellow cast; lips, pale; tongue, pale and dry; there is no icterus; no œdema; joints normal; no enlarged glands.

Thorax: Very large, broad, and deep. Breathing symmetrical. Physical examination of lungs negative.

Heart: Percussion unsatisfactory, on account of thick panniculus. There is a harsh, blowing systolic murmur in the pulmonary area, becoming softer, but audible, over other parts of the region.

Pulse: 120, soft, dicrotic.

Abdomen: Above level of ribs, pendulous. Large amount of fat makes examination difficult. Appetite fair; bowels constipated.

Blood: Thin and watery; red corpuscles, 1,120,000; leucocytes, 13,300; hæmoglobin (Fleischl), 25 per cent.

The urine contains neither albumin nor sugar.

14*th*. Examination of the eyes (Dr. Johnson): There are numerous retinal hemorrhages; several large ones, besides a general diapedesis from the sides of the arteries; great pallor of the eye-grounds.

The patient was treated locally in the throat and nose clinic, having been referred to the medical clinic for the blood-examination. As it was considered probable the blood-condition was the result rather than the cause of the bleeding, no change was made. The treatment consisted in the use of gelatin solution subcutaneously and in the nostrils, subsulphate of iron internally, and on several occasions, when the bleeding was profuse, plugging the nares.

The condition of the blood will be described in detail below.

The patient gradually became weaker, and had repeated hemorrhages, usually moderate, but more or less constant; leaking of blood from the nares when not plugged. Slight general œdema developed. Ecchymoses appeared in a few places on the skin. On January 24th slight icterus appeared, shown most plainly in the urine and scleræ, as the skin was yellowish on admission. On January 25th diarrhœa began, with tenesmus and frequent watery stools. On the 27th œdema of the lungs developed, the pulse became impalpable, and the patient died with increasing dyspnœa.

The *autopsy* was made an hour after death. I give here an abstract from the protocol of Dr. A. S. Warthin:

Anatomical diagnosis: Endothelioma carcinomatosum of turbinated bones; secondary anæmia; fatty infiltration of the liver with lymphoid infiltration; hyperplasia of spleen; fatty degeneration and liquefaction necrosis of heart-muscle with hemorrhages and lymphoid infiltration; broncho-pneumonia and œdema of the lungs; adenoma of prostate; simple hyperplasia of pancreas; arterio-sclerosis; slight icterus.

There is slight hypostatic congestion of the skin; skin and mucous membranes and scleræ pale-yellow; there is an ecchymosis the size of the hand on the right leg; also a small ecchymosis on the left arm. Panniculus very thick. Muscles brownish-red, large. All the tissues are very anæmic.

Examination of the skull and brain negative.

Diaphragm in the normal position. The left pleural cavity contains 300 c.c., the right 400 c.c., of cloudy fluid. The pericardium contains 400 c.c. of slightly brownish cloudy fluid. The membranes are smooth and shining, with numerous subserous hemorrhages.

The heart is large; weighs 694 grammes. All the chambers contain a great deal of thin fluid blood. There are numerous hemorrhages under the endocardium. The subpericardial fat is increased. The right auricle and ventricle contain pale ante-mortem clots. The tricuspid orifice admits three fingers. The left ventricle contains a small, pale ante-mortem clot and a small currant-jelly clot. The mitral orifice admits two fingers. There is a slight thickening of the mitral flaps. Otherwise the valves are negative.

The aorta shows moderate arterio-sclerosis.

The left lung contains air throughout, but exudes a turbid fluid from the cut surface. The right lung shows in the middle of the lower lobe an airless, dense, dark-red area of about $2\frac{1}{2}$ cm. in diameter; otherwise as the left.

The peritoneal cavity contains 200 c.c. of clear fluid. The omentum is very fat.

The spleen weighs 590 grammes. The capsule is tense, not thickened; the cut surface moderately red, slightly granular. Consistency firm, follicles enlarged, stroma increased.

The adrenals are negative. The left kidney weighs 199 grammes. The fatty capsule is excessive; the fibrous capsule not adherent, very smooth; the cut surface smooth, very pale; the glomeruli not dis-

tinct. The right kidney weighs 193 grammes; otherwise as the left. The ureters are negative. The bladder contains a large quantity of bile-colored urine; the mucosa is pale and thin, and shows small hemorrhages.

The stomach contains 400 c.c. of sour, grayish fluid, containing milk-curds. The mucosa is pale and appears atrophic. Small intestine and appendix negative. The rectum contains six or seven small ulcers covered with dirty-gray exudate.

The liver is much enlarged; weighs 3171 grammes. The surface is brownish-red; a flat furrow corresponds to edge of the ribs. Cut surface pale-yellow, very œdematous, greasy; consistency slightly increased. Lobules not distinct. Gall-bladder contains a small quantity of fluid bile.

The pancreas is large and pale.

The retroperitoneal and mesenteric glands are enlarged. All the vessels in the abdominal cavity show moderate arterio-sclerosis. The ribs, sternum, clavicle, skull-cap, and both humeri show no increase of red marrow. Both tibiæ when split show fatty marrow, gelatinous, with very small, scattered areas of lymphoid marrow of pale-pink color.

The peripheral vessels show moderate arterio-sclerosis.

Over both lower turbinated bones are small, soft, jelly-like growths, removed by curetting, as more extensive operation was not permitted.

These small tumors, which could not be detected during life, gave an explanation of the cause of the hemorrhage, and the other changes found are such as might easily be explained by the severe and repeated loss of blood. This was made more certain by the examination of the tissues, which were hardened in various ways, embedded, sectioned, and stained according to different methods.

Microscopic examination. Fatty degeneration and œdema occurred in all the organs to a greater or less degree. The serous membranes, especially in the heart, are the seats of hemorrhages, sometimes of considerable extent.

The growths from the turbinated bones show small alveoli filled with small cells having relatively little protoplasm, lying in a scanty, soft stroma. Secondary growths could not be found with certainty. In the heart, cells lying in rows occasionally suggest the nests of

the alveolar growth, but the same appearance might more readily be caused by the accidental arrangement of blood-cells between the muscle-fibres.

The heart, besides very extensive œdema and fatty infiltration and degeneration, and the subserous hemorrhages, shows a few small areas of small-celled infiltration, usually around vessels.

The liver is the seat of extensive fatty degeneration, especially in the inner parts of the lobules. The portal connective tissue is but slightly increased, but in most cases contains large numbers of small cells. There are also numerous foci of lymphoid tissue, in some cases growing centrally, with sharp outlines, and compression of the adjacent liver-cells, but usually diffuse, extending out in different directions and containing more or less well-preserved liver-cells in the peripheral areas. These areas reach or exceed the size of a single acinus. The capillaries are in many places dilated and contain blood like that obtained from the finger during life, but especially nucleated red corpuscles of all sizes. The well-preserved liver-cells on the periphery of the acini contain a large amount of brownish-yellow pigment, which gives the iron reaction with potassium ferrocyanide and hydrochloric acid. The lymphoid areas have a distinct, rather large meshed reticulum. They contain large numbers of large eosinophile cells with a single round or oval nucleus, a few eosinophile cells with irregular nuclei, leucocytes of various kinds, mostly mononuclear, and nucleated red corpuscles of various sizes. The appearance of these areas is not unlike that of bone-marrow in cases of mixed-celled leukæmia, but the number of eosinophile cells is even greater than is common in such bone-marrow.

The kidneys show slight thickening in the walls of the arteries. A few glomeruli are partly or wholly fibroid. The epithelium is well preserved for the most part. The convoluted tubules are slightly dilated. There are very few areas of lymphoid infiltration, irregular in outline, diffuse, containing large numbers of eosinophile cells and other leucocytes.

The spleen shows an increase of lymphoid cells in the parenchyma. In the latter the capillaries are often wide, and there are large numbers of eosinophile cells, mostly large and mononucleated, nucleated red corpuscles, and large mononuclear leucocytes.

The lymph-glands show chronic hyperplasia. The sinuses are

distinct, contain large numbers of epithelioid cells, but there is no excess of the eosinophile and nucleated red corpuscles.

In the bone-marrow sections from the small lymphoid area show much of the original fat, with small islands irregular in size and outline. These contain large numbers of eosinophile cells, largely mononuclear, mononuclear cells of various sizes with neutrophile granules, nucleated red corpuscles of all sizes, small numbers of cells of the types of lymphocytes and polynuclear cells, and a few polynuclear giant-cells. These lie in a reticulum, and at times in capillaries or larger thin-walled vessels.

Cover-glass preparations from the lymphoid marrow show many nucleated red corpuscles of all sizes and free nuclei, small and deeply staining. The nuclei in the red cells are rather more irregular than in the peripheral blood and have a looser arrangement of the chromatin; the protoplasm rarely shows polychromatophilia. The leucocytes in these preparations show no variations from those common in red marrow.

In order to interpret the changes described we must consider more in detail the phenomena observed in the blood during life.

After admission the red corpuscles fell considerably and reached the minimum a week after (January 20th), with red corpuscles, 357,600; Fleischl, 20 per cent. The next day, however, the red corpuscles rose to 820,000, and remained about the same, falling to 760,000 two days before death. The leucocytes, moderately increased (13,300) on admission, numbered 30,500 on the 17th, 49,656 on the 20th, 48,000 the 21st, and 35,000 the 25th. The blood was examined microscopically daily, and differential counts of the leucocytes and the nucleated reds made almost daily. It was difficult to estimate the leucocytes accurately in the hæmacytometer on account of the confusion with nucleated red corpuscles, and there is a considerable error for that reason, but one that in the case of the leucocytes is not of material importance. It would have been better to have counted all nucleated cells in the blood-counter and then to have made out the proportion of white to red in dried preparations. In this, however, there would still have been the possibility of error from the overlooking of the smaller nuclei in the blood-counter.

The leucocytes show slight but interesting anomalies.

The small lymphocytes varied at times, but were never excessive.

On January 12th there were 6.2 per cent.; 16th, 2.1; 19th, 2.7; 22d, 6.9; 25th, 7.9.

The large lymphocytes—*i. e.*, those larger than average red cells, and with paler nuclei and more protoplasm than the preceding—numbered: January 12th, 21.4 per cent.; 16th, 14.1; 19th, 27.2; 22d, 25.7; 25th, 23.5.

The polynuclear (neutrophile) cells, varying more in size than normal, but otherwise not remarkable, numbered on the same days: 67.3, 69, 60.1, 54, and 57.2 per cent.

The polynuclear eosinophile cells formed on the respective days: 2.6, 2.5, 3.3, 2.3, and 1.8 per cent. They presented no peculiarities of structure, though varying in size among themselves, and were rarely degenerated. Mononuclear eosinophile cells were always present, but often not numerous enough to appear within the ca. 1000 leucocytes counted. Twice (January 12th and 22d) they reached 3 per 1000 and once (25th) 4. They were usually large, with round or oval nuclei.

Cells with basophile granulations (methylene-blue) were always present to the extent of about 1 per cent.

Myelocytes (of Ehrlich) were always present, but not very numerous—0.3 to 3 per cent.—up to the week before death. They then reached 9.7 per cent., and amounted to 7 per cent. the day before the last. They showed characteristic staining properties and varied considerably in size.

Degenerated cells, usually only the nuclei, polymorphous, or round, were present to the extent of about 1.5 per cent.

On the whole, the leucocytes show simply a total increase of all forms, with such abnormal varieties as occur from an excess from different causes. No example of mitosis was found among these cells.

The red corpuscles present more interesting features. In size they are, for the most part, normal or slightly below (about 7 μ measured dry), but there are a few large ones, up to 10 μ, and a few small ones. Very small cells, such as occur in pernicious anæmia, are extremely rare. Poikilocytes are not numerous, but evidences of protoplasmic degeneration, such as fissures, vacuoles, and coarse granular appearance, are not uncommon.

Variations in the staining of the red corpuscles are also frequent. Shadows, not taking any stain at all, are occasionally found, and

between them and cells taking a normal stain are all varieties. Polychromatophilia in the non-nucleated cells is also occasionally seen.

The most important feature in the blood is the enormous number of nucleated red corpuscles. Considering the source of error mentioned above, there were on admission from 2370 to 2840 per c.mm. —that is, if only leucocytes were counted as such, there were 2840 nucleated red corpuscles per c.mm—if all the nucleated reds were counted as leucocytes, there were 2370 nucleated reds per c.mm. The real number lies between the two. In five days, with a leucocyte count of 30,500, the proportion was even higher—21 instead of 18 per cent.—so that the maximum count of nucleated reds on that day would be 7320, the minimum 6543. With the maximum leucocyte count of 49,656, the proportion of nucleated reds to all nucleated cells was 37 per cent. This would give 18,372 red corpuscles; but if the reds were all excluded in the leucocyte count there would be at that time 26,391 nucleated reds. At the last count, with 35,000 leucocytes, there were 33 per cent. of nucleated reds, or 11,555, with a maximum of 17,712. Even the minimum figures show a very unusual condition. I have once before seen nucleated red corpuscles in the same relative proportion to leucocytes, but in that case there was a low leucocyte count. Von Noorden, in the case in which he first noticed the now well-known blood crisis, counted as many as seven nucleated red cells in a field of the oil-immersion lens. In my preparations it is not uncommon to find as many as ten or twelve to a field in a very thinly spread preparation.

A few free nuclei, usually easy to distinguish from the small lymphocytes, are always present. Sometimes these have a very thin hæmoglobin rim.

In size of body the nucleated corpuscles vary from 5 μ to 15 μ. One in mitosis measures 17.5 μ by 13.6 μ. The nuclei show all varieties, from the small, deeply staining and compact form to the pale and large one, often showing a well-marked chromatin network, and those in indirect division. The small nuclei, of normoblast type, are always more numerous, and are most frequently found in cells about the size of normal red cells, though they sometimes occur in much larger ones. Irregular nuclei, in trefoil, or ace of clubs, or rosette figures, are numerous; often the nuclei are near or overlap the edges, and in many

cells the nuclei are broken into numerous irregular bits, and in some cases the escaping nucleus has a distinct rim of hæmoglobin.

Measuring and counting 500 successive nucleated red cells (January 19th) I found 48 over 10 μ in diameter. Fifteen of them had small, compact, or lobulated nuclei. The other 33 had nuclei of the typical megaloblast type. These are relatively large, round, or elliptical, often eccentric, but never protruding from the body, with the chromatin in a more or less distinct meshwork, in which the nodal points are often well marked. Cells having nuclei of this type, but less than 10 μ in diameter, are common. Out of the above 500, 23 were of this variety.

Mitotic figures can be found in the red corpuscles in all preparations, and in some one can find four to six in a single cover-glass. I allude only to distinct karyokinetic figures. There are always cells with the chromatin in granules or rods, or in a mass suggesting an equatorial plate, but these I have not counted as mitoses. Those found are almost all in the later stages, with disasters, and sometimes beginning division of the protoplasm. Very often two nucleated cells may be seen close together, suggesting recent division; but this is likely to be accidental, as one can also find groups of three, four, or even more, side by side.

The large number of nucleated red corpuscles in this case enabled me to confirm an observation I made several years ago—viz., that the nuclei of the red cells undergo changes of size and shape in the fresh drop under the cover-glass. When I first saw this I supposed it was an optical illusion from the movement of the nucleus out of focus, but careful observation proved this not to be the case. The process was always seen in the small nuclei in rather large cells. It consists in a slow, at times rather rhythmical, contraction and expansion, with changes from round to oval and back to round, and change in position in the corpuscle. The various changes can be seen within two or three minutes. That such changes occur has long been known to histologists. It does not seem, however, they are taken into account in discussions regarding the size and structure of nuclei. Differences in the appearance of the larger nuclei also occur in the fresh drop, but I did not have time nor opportunity to watch the corpuscles long enough to see the process of indirect cell division, as did Askanazy (*Zeitschrift für klin. Med.*, Bd. xxiii. p. 90). I made an effort to

obtain evidence of both processes by keeping freshly spread covers in the moist chamber at 37° C., and fixing them by alcohol and ether at intervals. In preparations made in this way I found that in blood containing a large number of normoblasts the nuclei were on the average larger and showed a more distinct meshwork ten minutes after removal. At fifteen minutes they were smaller again. After twenty minutes the cells began to break down, the nuclei swelled, stained deeply on the periphery and faintly in the centre. Mitosis was not more common in the preparations than in those dried quickly.

The protoplasm of the nucleated cells shows important staining characteristics. In many cases the protoplasm takes a more or less marked blue from hæmatoxylin, either diffuse or in fine meshwork, or very rarely in fine granules. With Ehrlich's triacid stain such cells take a darker color than the rule. Some of these cells are evidently erythroblasts of Löwit. Polychromatophilia is most commonly found in the megaloblasts of all sizes, but also occurs in cells of true normoblast type. In many dividing cells, and in some with very large nuclei and narrow protoplasm, the latter takes a uniform pale blue color with hæmatoxylin, not unlike that in certain leucocytes, and, in in fact, many of the cells with indirect nuclear division closely resemble dividing myelocytes. I have never, however, found the nuclei in the blood-cells in the present case precisely like those in myelocytes as one sees them in leukæmic blood and in bone-marrow.

In a few cells there is a sharp demarcation, sometimes even a fissure, separating the part of the protoplasm that takes the basic stain from the inner acidophile part.

In the interpretation of the case the most obvious fact appears to be that the striking changes found in the liver, spleen, and bone-marrow are closely connected with regeneration of the blood following hemorrhage. Neither the nasal tumor nor its secondary results can directly account for these.

The important features about the changes are that those in the bone-marrow are relatively slight, those in the spleen, as usual, difficult to determine, and those in the liver unusual and striking. I do not know of a similar observation. It is noteworthy that the capillaries of the liver, on the whole, do not present such marked evidence of blood formation there as is seen in many anæmic diseases, but the process occupies large foci.

The case also illustrates the practical impossibility of making a sharp distinction between normoblasts and megaloblasts, and strengthens the opinion I have formed from other cases, that a morphological difference does not exist, agreeing thus with the views of Askanazy, Schaumann, and Dunin. The convenience of the term megaloblast, however, is undeniable, and the occurrence of transitions to normoblasts only adds to the interests of the former bodies.

To the question whether the megaloblasts are young or old cells—still an open one—I think the answer must be that they are young. This view is based on the structure of the nucleus, and on the frequency of mitoses in these cells. So far as the polychromatophilia is concerned, this is no doubt often an evidence of degeneration, but as Gabritscheowsky has well remarked, degeneration would be likely to affect young and unformed cells.

Those who share Ehrlich's view as to the nature and significance of megaloblasts will no doubt look on the fatal outcome in this case as proof of their theory. It certainly is a most remarkable fact, that in spite of the extent of blood formation the actual renewal of the patient's blood did not take place, and, although it is hardly safe to draw sweeping conclusions from the case, one is almost forced to believe that, notwithstanding the morphological relationship of the cells, there is a connection between the megaloblastic alteration of the blood-forming organs and the failure to produce good blood. The causes and nature of the change remain as most important and interesting problems.

DISCUSSION.

DR. THAYER: I saw about six years ago a case that in certain respects bore some resemblance to that described by Dr. Dock. It was a case of fatal anæmia in a man between fifty and sixty years of age, where the blood showed enormous numbers of nucleated red corpuscles, apparently as many as in this case. They differed, however, in character, in that they were all of small size, with small, deeply staining nuclei; there were absolutely no megaloblasts. In that case there was a progressive anæmia, ending fatally. There was a great excess of small mononuclear leucocytes. The leucocytes were increased in number, at one time reaching as high a figure as 80,000 to the cubic millimetre, so that the picture was almost that of a lymphatic

leukæmia. Unquestionably fatal cases of anæmia may occur where the nucleated red blood-corpuscles in the circulating blood are all of a normoblastic type.

DR. STENGEL: In the examinations of the blood of post-hemorrhagic cases that I have made normoblasts and microblasts have been the forms of red corpuscles that were discovered; but I have never seen a case in which there was anything like the number of nucleated red cells that occurred in Dr. Dock's and Dr. Thayer's cases. I agree with Dr. Dock that no sharp line can be drawn between the different types of red corpuscles. They seem to me to be variations which merge into each other without any sharp distinctions. I cannot agree, however, with him, as far as prognosis is concerned, that there is any significance either in the mere presence or the kind of nucleated red corpuscles. Some have gone so far as to say that the diagnosis of pernicious anæmia could not be established in a case in which the microblasts were present in great excess of the megaloblasts, but I am sure that this is not sound teaching. I have myself observed cases of pernicious anæmia in which there were many nucleated red corpuscles, most of them being of small type, and similar instances might be cited from medical literature. The nucleated red corpuscles seemed to me to be evidences of regeneration of the blood, but whether this regeneration is sufficient to preserve life or not must be judged in other ways than by the mere inspection of the blood.

DR. OSLER: I would like to mention a very remarkable form of epistaxis and to ask the members present if they have had any experience with it. I have had three instances of it developing in early manhood, proving nearly fatal, and associated with the most remarkable development of angiomata over the surface of the skin. Two of these cases were in brothers, and one case died recently of cancer of the stomach, and showed these remarkably large veins from which the bleeding had occurred in the nose. The picture presented by one of the cases was peculiar in that as you looked at him across the room you would think he had a case of acne. I could find no reference to such a condition in literature, and it was interesting to note the association between the varices of the mucous membrane of the nose and the cutaneous angioma.